

PTO upon the filing of the application. Copies of the cover letter and returned post card are attached to this Response. Applicants would appreciate the examiners guidance upon the proper procedure for submitting another copy of the software appendix if the examiner is unable to locate the original at the Patent Office.

Response to New Claim Rejections Under 35 USC §112

The examiner has rejected claims 1-3 under 35 USC §112 "...because the specification, while being enabling for methods as outlined below, does not reasonably provide enablement for determining pka for all molecules encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims." The examiner suggests that the method "...is not considered to be so predictable that the method as claimed could be extrapolated to ... larger and more complex molecules" with many ionizable sites such as proteinaceous polymers and polynucleotide polymers. Applicants respectfully disagree with the position taken by the examiner and present the following argument in support of their position.

First, the examiner acknowledges that applicants have enabled the method for some molecules of interest. However, the examiner has taken the position that there might be 'other molecules of interest' which might be chosen by a user for which the method of the invention will not yield an accurate estimation of pK_a . Following this logic, the examiner would find non-enabled any patent method claim for which an example is found for which the method of the claim does not work, despite the fact that the method works for a broad range of examples. Applicants submit that this position is incorrect. Having enabled the

invention covering a broad range of molecules, applicants are entitled to claim their invention broadly.

Whether the examiner agrees or disagrees with the above position, applicants submit that there is yet a more fundamental reason that the claims should not be rejected. Specifically, applicants submit that the examiner's characterization and/or appreciation of the level of skill of those persons skilled in the art is in error. Applicants submit that persons reasonably skilled in the art would recognize the molecules to which the method could and could not be applied. For instance, using the examiner's examples, at some level of complexity these molecules (proteinaceous and polynucleotide polymers) assume a three dimensional confirmation in which non-adjacent elements are brought in close enough proximity to strongly influence the micro-environment of an ionizable site. It is well understood in the art that such three dimensionally induced permutations of the micro-environment influence the ability to accurately calculate a pK_a . It is further understood in the art that three dimensional considerations are not limited to polymeric molecules. For instance, the cis and trans conformational isomers of smaller molecules may differentially locate groups so as to influence the micro-environment of an ionizable site on the molecule. Thus, an accurate estimate of pK_a could be obtained for one conformational isomer and not the other.

Those skilled in the art are familiar with the consequences of the three dimensionality of the molecules of interest. Accordingly, those skilled in the art would, in fact, recognize those molecules with which the invention could be used and those molecules with which the invention could not be used. Those skilled in the art could use the invention commensurate

with the scope of the claims. Applicants respectfully submit that the enablement requirements of 35 USC 112 are fully met as being enabling to those person reasonably skilled in the art. Accordingly, Applicants request that the Examiner withdraw the 35 US C §112 rejection.

The examiner has also included two additional comments in the rejection. First, the examiner states that: "It is noted that the claims do not require that the molecules of known pK_a in step (a) to be in any way related to the molecule of interest whose pK_a is to be predicted." Second, the examiner states: "It is further noted that while the specification indicates that five levels produce good results (see page 5), in complex molecules it would appear that many more levels would be required thereby increasing the degree of computational difficulty." Applicants do not believe that these comments by the examiner are directed to the grounds of rejection, but are simply observations not requiring a response by applicants. If applicants have misunderstood the examiner, applicants would appreciate further comment by the examiner so that applicants can prepare a proper response.

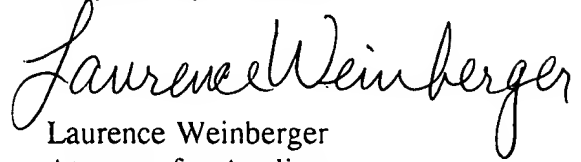
Finally, the examiner has noted that there is a commercially available software product from CompuDrug which has a module called *pkalc* and has attached pages from the compudrug.com web site describing the product. Applicants have been encouraged to provide information about this product available to applicants. In the second full paragraph on the web page found at URL <http://www.compudrug.com/pkalc.html> it is noted that the software uses *Hammett and Taft* equations to perform the calculation of pK_a . The use of these equations is well known in the field and is an entirely different approach to the determination of pK_a that the approach of the present invention.

Applicants submit that they have responded to and overcome all grounds for rejection

set forth by the Examiner and respectfully request that the Examiner allow the application and pass it to publication.

October 8, 2002

Respectfully submitted,

A handwritten signature in cursive script that reads "Laurence Weinberger". The signature is written in black ink and is positioned above the printed contact information.

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